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Functional and dysfunctional impulsivities changes after subthalamic nucleus-deep brain stimulation in Parkinson disease

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TITLE: FUNCTIONAL AND DYSFUNCTIONAL IMPULSIVITIES CHANGES AFTER SUBTHALAMIC NUCLEUS-DEEP BRAIN STIMULATION IN PARKINSON DISEASE.

TITRE EN FRANÇAIS : VARIATIONS DE L'IMPULSIVITE FONCTIONNELLE ET DYSFONCTIONNELLE APRES STIMULATION CEREBRALE PROFONDE DES NOYAUX SOUS-THALAMIQUES DANS LA MALADIE DE PARKINSON.

Running title: Functional / dysfunctional impulsivity in DBS

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3) Manuscript: A. Writing or the first draft, B. Review and critique

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RESUME :

Objectifs : Evaluer les variations de l'impulsivité chez des patients parkinsoniens opérés par stimulation cérébrale profonde des noyaux sous-thalamiques (SCP-NST) en distinguant l'impulsivité fonctionnelle (IF) et l'impulsivité dysfonctionnelle (ID).

Méthodologie : Les données pré et post opératoires à 6 mois de 33 patients avec maladie de Parkinson idiopathique traités par SCP-NST ont été étudiés: la sévérité de l'atteinte motrice, les traitements, les fonctions cognitives, l'apathie et l'humeur, et les troubles du contrôle des pulsions. L'échelle de Dickman permettait d'évaluer deux dimensions de l'impulsivité: l'IF reflétant le potentiel de réflexion et d'action rapide quand la situation l'exige, et l>ID reflétant l'absence de réflexion préalable à l'action quand la situation le demande. La localisation des contacts stimulants dans le NST a été étudié à l'aide d'un atlas histologique déformable et par compartimentation du NST, à partir de l'IRM postopératoire.

Résultats : Après 6 mois de stimulation, l>ID avait significativement augmenté ($p < 0,001$) (pré : 1,9 +/-1,6 et post : 3,5 +/-2,4) sans modification de l'IF (pré : 6,2 +/-2,7 et post : 5,8 +/-2,6). L'augmentation de l>ID était liée à : un score BREF pré-opératoire bas ($p = 0,03$) et la position du contact actif gauche dans la partie inférieure du NST ($p = 0,012$).

Conclusion : Notre étude suggère que la SCP-NST influencerait de manière différente sur les deux dimensions de l'impulsivité, en aggravant l'impulsivité pathologique (ID) sans modifier l'impulsivité physiologique (IF). L'augmentation de l>ID pourrait être favorisée par la localisation de l'électrode dans la partie inférieure, limbique, du NST.

Mots clés : “Maladie de Parkinson” ; “Impulsivité” ; “Stimulation cérébrale profonde” ; “Noyaux sous-thalamiques” ; “Troubles du contrôle des pulsions”.

ABSTRACT

Objectives: We investigated changes of impulsivity after deep brain stimulation (DBS) of the subthalamic nucleus (STN) in Parkinson's disease (PD) patients, distinguishing functional from dysfunctional impulsivity and their contributing factors.

Methods: Data of 33 PD patients treated by STN-DBS were studied before and 6 months after surgery: motor impairment, medication (dose and dopaminergic agonists), cognition, mood and occurrence of impulse control disorders. Impulsivity was assessed by the Dickman Impulsivity Inventory, which distinguishes functional impulsivity (FI), reflecting the potential for reasoning and rapid action when the situation requires it, and dysfunctional impulsivity (DI), reflecting the lack of prior reasoning, even when the situation demands it. The location of DBS leads was studied on postoperative MRI using a deformable histological atlas and by compartmentalization of the STN.

Results: After STN-DBS, DI was significantly increased (mean pre- and postoperative DI scores 1.9 +/-1.6 and 3.5 +/-2.4, $p < 0.001$) although FI was not modified (mean pre- and postoperative FI scores 6.2 +/-2.7 and 5.8 +/-2.6). Factors associated with a DI score's increase ≥ 2 (multivariable logistic regression model) were: low pre-operative Frontal Assessment Battery score and location of the left active contact in the ventral part of the STN.

Conclusion: Our study suggests that STN-DBS may have a different impact on both dimensions of impulsivity, worsening pathological impulsivity without altering physiological impulsivity. The increase in dysfunctional impulsivity may be favoured by the location of the electrode in the ventral part of the STN.

Key words: "Parkinson's Disease"; "Impulsivity"; "Deep Brain Stimulation"; "Subthalamic Nucleus"; "Impulse Control Disorder".

1. INTRODUCTION

Deep brain stimulation (DBS) of the subthalamic nucleus (STN) is routinely used to treat motor complications in Parkinson's disease (PD) [1]. STN is part of the motor, cognitive and affective cortico-subcortical circuits [2]. STN plays an essential role in decision-making and especially to send "hold your horses" or "no-go" signal to slow down when faced with decision conflict, to allow time to gather and integrate multidimensional information before decision is made [3-5]. Consequently, alteration of STN activity by STN-DBS is predicted to result in impulsive responding when faced with conflict [4]. However, the impact of STN-DBS on impulsivity in PD patients is controversial [4, 5]. Some studies reported no influence or improvement of impulsivity after STN-DBS [6-8], although other demonstrated that impulsivity appeared or worsened after DBS [3, 9-12]. Discrepancies between these studies may result from several contributing factors including medication and methods used to evaluate the impulsivity. Most of the previous studies have used the occurrence of Impulse Control Disorder (ICD) or hyperdopaminergic behaviours, which are acute events, to evaluate impulsivity and only few studies have used impulsivity scales. Moreover, impulsivity is a multidimensional phenomenon and STN-DBS may affect differently these dimensions of impulsivity [13]. All the scales used in DBS studies consider impulsivity as a negative trait. However, the consequences of impulsivity are not always negative, as for example when the time available for making a decision is extremely brief, high impulsives are actually more accurate than low impulsives. To provide original data to this debate, we studied impulsivity changes after STN-DBS and their contributing factors in PD patients by using the Dickman Impulsivity Inventory, which distinguishes functional impulsivity (FI), reflecting the potential for rapid response when the situation

requires it, and dysfunctional impulsivity (DI) reflecting the lack of prior reasoning to action, even when the situation requires it.

2. METHODS

2.1. Patients

We studied retrospectively pre- and postoperative data of 33 consecutive patients treated in our institution by bilateral deep brain stimulation of the subthalamic nucleus (STN). Patients included suffered from idiopathic Parkinson's disease at the stage of motor complications of dopa therapy, for more than 4 years, treated with bilateral STN stimulation, without surgical complication, with complete impulsivity assessment before and after surgery and post-operative MRI.

DBS leads were implanted stereotactically under local anaesthesia and then connected to the generator under general anaesthesia. STN targeting was performed using indirect localization relative to bi-commissural plan on gadolinium-enhanced 3D T1-weighted MR sequence, then refined by direct visualization on T2-weighted MRI sequence. Final lead implantation was guided by microelectrode recordings (2-5 tracts/side) and intra-operative clinical testing to assess stimulation-induced PD symptoms improvement and side effects.

2.2. Evaluation

Assessment was part of the usual complete pre- and post-operative evaluation and included motor, cognitive, behavioural and psychiatric examination, and post-operative 3D MRI. Patients were assessed on-medication before the operation and on-medication on-stimulation after DBS. The following data were collected for each patient before and

6 months after surgery: age, sex, duration of disease progression, psychiatric history (since the beginning of the disease), severity of motor impairment (UPDRS III score on and off medication) and anti-parkinsonian treatment (Levodopa equivalent dose (LED) and dopaminergic agonists intake). Cognitive functions were evaluated by the Mattis dementia rating scale, the Frontal Assessment Battery score (FAB) and its Go-No Go test sub-score [14]. Psychiatric and behavioural evaluation included an interview with a psychiatrist, the assessment of apathy using the apathy inventory (AI) [15], depression by the Montgomery and Asberg Depression Rating Scale (MADRS) [16] and the occurrence of impulse control disorders (ICD) during the 6 month-periods before and after surgery, using the Ardouin Scale of Behaviour in Parkinson's Disease [17]. Impulsivity before and after DBS was also assessed using the French short version of the Dickman Impulsivity Inventory (DII) [18, 19]. The DII is a self-report questionnaire developed to measure two types of impulsivity, namely Functional and Dysfunctional Impulsivity. Dysfunctional impulsivity is defined as the tendency to act with less forethought than most people of equal ability when this tendency is a source of problems. Functional impulsivity is defined as the tendency to act with relatively little forethought when such a style is optimal. In the DII, these 2 types of impulsivity are graduated on a continuum ranging from 1 to 11 (for FI) and from 1 to 12 (for DI). For FI, the higher the score, the more suitable is the patient. On the contrary, regarding the DI, the lower the score, the more adapted is the patient. FI and DI scores are normally distributed in the general population. The DI mean values vary between 1,8 and 3,7 in the general population, varying across gender and ages, increased to 6,8 in average in drug addicts and suicide victims [19-22]. The mean value in the French general population is 2,85 +/- 2,76 [19]. However Dickman and Caci did not define a threshold

for abnormal value or significant variation [18, 19]. Based on these data and our clinical experience, we measured changes in FI and DI and considered a variation greater than 2 points as clinically significant for identification of factors of variation.

2.3. Location of the stimulating contacts of the electrodes

For each patient and each electrode, we identified the stimulating contact used during the 6 months preceding the postoperative assessment and whose stimulation had led to the best clinical improvement. The anatomical location of these contacts was studied from postoperative MRI after registration and fusion on the 3D deformable histological atlas of the basal ganglia [23]. This atlas adds histological information, non-existent in the MRI, as well as the delimitation of the different functional subdivisions of the basal ganglia: a motor area (dorso-lateral), targeted in PD, a limbic area (antero-medial and ventral) and an associative area, between these two. Moreover, we segmented the STN into 2 planes (Figure 1), to delimit several regions: ventral and dorsal, lateral and medial, anterior and posterior. The location of right and left stimulating contacts within the STN has been studied according to their position in the functional subdivisions and according to these plans.

2.4. Statistical analysis

Statistics were computed using Stata (version 12, StataCorp, College Station, USA). All tests were two-sided and a p-value <5% was considered as statistically significant. Study sample is described by numbers and associated percentage for categorical data and by mean \pm standard deviation or median [interquartile range] when data not normal for continuous data. Normality was assessed graphically and using the Shapiro Wilk's

test. Difference in FI and DI were computed (after-before stimulation) and dichotomized as increased vs stable+decreased and analysed to find factors that were associated with changes. This analysis was performed using chisquared test (or Fisher's exact test when appropriate) for categorical data, and using Student's t test (or Mann and Whitney's test when normality not reach) for continuous data. A multivariable logistic regression model was performed, adjusted on covariates that were highlighted with a $p < 0.15$ in the univariate analysis. A backward selection method was applied with removal when $p\text{-value} < 0.15$. Results are shown as adjusted odd ratio and their 95% confidence interval. No other model but the two analysing evolution of the DI and FI were computed.

3. RESULTS

3.1. Patients

Thirty-three PD patients were included (20 men). Mean age at the time of surgery was 59 years (± 9.2 years). Mean disease duration was 10.3 years (± 6.1). Other patient's characteristics are detailed in table I. A psychiatric history was found in 82% ($n=27$) of patients: depression ($n=18$), anxiety disorders ($n=14$), hypomanic episode ($n=1$), suicide attempt ($n=1$), addiction ($n=1$), delusional or hallucinatory episode under dopaminergic treatment ($n=1$). Fourteen patients had ICD or other hyperdopaminergic disorders in the 6 month-period prior to preoperative assessment: pathological gambling (5), hypersexuality (6), compulsive buying (4), eating disorder (9), as well as punding (2), nocturnal agitation (6), dopaminergic dysregulation syndrome (2). Mean functional impulsivity (FI) and dysfunctional (DI) scores on the DII were 6.24 ± 2.68 and 1.93 ± 1.64 respectively before surgery (Table II). Twelve out of 33 patients had a DI score \geq

3 before DBS. We observed no correlation between preoperative FI and DI scores and preoperative occurrence of ICD ($p=0.66$ and 0.13 respectively).

3.2. Postoperative outcome

After 6 months of stimulation, we observed a significant ($p<0.001$) increase in dysfunctional impulsivity (mean postoperative DI score was 3.48 ± 2.40), whereas functional impulsivity (mean postoperative FI score 5.75 ± 2.61) was not significantly changed (Table 2). Twenty out of 33 patients had a DI score ≥ 3 after DBS. Eighteen patients had a ≥ 2 increase in the DI score after the intervention compared to baseline, while only 2 had a ≥ 2 decrease in this score. During the 6 months-period after surgery, 14 patients presented one or several ICD: pathological gambling (2), hypersexuality (3), compulsive buying (4), hyperphagia (8), nocturnal agitation (5). Of the 19 patients who had no prior history of ICD before intervention, 6 (31.6%) presented one after DBS. Eight out of the 14 patients who had had an ICD before surgery (57%) had an ICD after DBS. We did not observe a significant relation between the presence of preoperative ICD and the occurrence of postoperative ICD ($p=0.14$) and there was no correlation between post-operative FI and DI scores and postoperative occurrence of ICD ($p=0.19$ and 0.57 respectively). Postoperative LED was 564 ± 381 after DBS and 17 patients used dopaminergic agonists. We observed no significant change in the Go-No Go test scores before and after DBS.

3.3. Predictive factors

Factors associated with a DI score increase ≥ 2 points after DBS compared to baseline were (table III): preoperative low score on the FAB scale and the location of the left

active contact in the ventral part of the STN (Figure 1). Indeed, 11 out of 33 patients with a significant DI increase had their stimulating contacts into the ventral part of the left STN. Moreover, 8 out of 14 patients with post-operative ICD had their stimulating contacts into the ventral part of the STN. Age, high pre-operative UPDRS III On medication score and preoperative low Go-No Go score were related to DI worsening in univariate analysis only. Factors that tended to be associated with a FI score increase ≥ 2 were: a high preoperative apathy (AI score), and a frontal impairment (low FAB score). In contrast, the DI and FI changes were not associated with other preoperative factors such as: gender, psychiatric history, preoperative occurrence of ICD, Mattis and MADRS scores, and contact location according to Yelnik atlas functional subdivisions. We observed no correlation between pre-and post-operative Go-No Go scores and pre-and post-operative FI and DI scores. Despite postoperative medication decrease after DBS, pre-and post-operative LED, pre- and post-operative dopaminergic agonists intake were not related significantly to impulsivity changes.

4. DISCUSSION

In our study, dysfunctional impulsivity increased significantly after STN-DBS in PD patients, but functional impulsivity (FI) did not change significantly. Factors associated with this DI increase were a low preoperative FAB score and left active contact location in the ventral STN.

These findings provide new insights into the current and highly controversial debate about the influence of STN-DBS on impulsivity and the disorders associated with its variations, including Impulse Control Disorders (ICD). The STN is involved in cortico-subcortical motor networks, but also cognitive and emotional networks. STN appears

essential to allow all information to be integrated before decision-making, and its role would be to prevent premature, impulsive responses, especially in high-conflict situations: this is referred to a « hold your horses » signal allowing to delay the decision and gather additional information to choose the best option [3, 11].

Numerous studies suggest that STN-DBS increases impulsivity in operated PD patients [3, 9-12, 24]. Therefore, the surgical indication might be questioned in case of significant preoperative impulsivity or ICD in PD patients applying for DBS. On the opposite, several studies report no change or improvement in impulsivity or impulsive behaviours [6-8]. Lhommée et al. showed in a recent large study that hyperdopaminergic behavioural disorders, and in particular some ICD (nocturnal hyperactivity, creativity, hobbyism, hypersexuality) improved after STN-DBS in comparison with the preoperative state and in comparison with a similar group PD patients treated by medication only [6]. Other ICD such as pathological gambling, compulsive shopping and food compulsions were not altered by the STN-DBS. These findings suggest that the presence of ICD in a PD patient would be a good indication of STN-DBS because they might be improved after surgery.

The relations between ICD and impulsivity, although apparently obvious, seem actually more complex. Studies have correlated the occurrence of ICD with an increase in impulsivity, but this direct relationship has been criticized [12, 25]. Though it is not the only mechanism explaining it, impulsivity may be a pathophysiological mechanism underlying the onset of ICD [26]. A dual etiopathogenic pathway toward the development of ICD has been proposed with one of the two gateways being high impulsive traits producing a positive reinforcement mechanism that triggers the occurrence of ICD [27]. However, most studies have evaluated changes in impulsivity

based on the ICD onset frequency [6, 8, 9], from motor inhibition tasks [11, 24], reaction time such as the Simon Task [28], decision-making tests [3], or risk tests [29]. Few studies only have evaluated impulsivity by using specific impulsivity scales, such as the UPPS (Urgency Premeditation, Perseverance, Sensation Seeking impulsive behaviour scale) [12] or the Barratt Scale [10]. The Barratt Impulsiveness Scale considers impulsivity as a personality feature. This self-report questionnaire explores different dimensions of impulsivity, the motor impulsivity (tendency to immediately react to a stimulus without reflection), cognitive/attentional impulsivity (tendency for fast decision-making and associated attentional difficulties) and the non-planning impulsivity (lack of premeditation). In their study of 53 PD patients, Halbig et al. noticed that the overall impulsivity Barratt score increased after STN-DBS [10].

We preferred to use the Dickman Impulsivity Inventory (DII), another self-report questionnaire specific to impulsivity, because it evaluates two dimensions of impulsivity: functional impulsivity and dysfunctional impulsivity [18]. FI characterizes the ability for a person to take the time to think and premeditate his action, with the possibility of acting quickly by using the best possible strategies according to the situation. On the opposite, DI is the incapacity for a subject to take the time necessary for reflection required by the situation. The model of impulsivity proposed by Dickman allows an overall understanding of impulsivity, considering the FI as physiological (premature but adapted response), and the DI as pathological (premature and not adapted response). Unlike other scales, the DII allows impulsivity to be approached as a concept that is not only negative. It also makes it possible to distinguish specifically the variations of the DI, which may be involved in the occurrence of ICD. In our study, we observed distinct changes of these two dimensions: DI was worsened after STN-DBS,

whereas the FI was unchanged. This distinct influence of STN-DBS on distinct impulsivity dimensions might contribute to the discordance of studies previously published in this domain.

However, the DII has two limitations. On one hand, it relies on self-assessment, which exposes to the risk of declarative bias that is however tampered by the presence of a patient's relative during the behavioural evaluation. On the other hand, although it has been validated in numerous studies and in a French version, this scale is not specific to PD. Moreover, the DII expresses impulsivity as a continuum from normal to pathological and there is no defined pathological threshold. For the analysis of factors predicting impulsivity changes, we arbitrarily chose to consider as significant a 2-point change in FI or DI because in our experience, such variation is clinically significant. However a possible re-test effect could be discussed. The temporal stability of the DII has been evaluated after a 12-month re-test in the French population and showed no statistical difference [19].

We observed several factors that tended to be associated with a postoperative ≥ 2 points increase in FI, including the severity of apathy and the frontal impairment (low FAB score) before surgery. In PD patients, higher apathy is a sign of hypodopaminergic functioning, which can be modulated by dopaminergic treatments, especially in cases of severe mesolimbic denervation [25]. Severe mesolimbic denervation may be related to a risk of inhibition relief in these patients who are very sensitive to dopaminergic stimulation and STN-DBS. This could explain why, in our study, FI increased more after DBS in the more apathetic patients. The FAB scale allows rapid assessment of executive functions, which are involved in situations that require the subject to think, anticipate, and adapt. This scale includes a Go-No Go test evaluating the inhibitory

control, whose dysfunction can result in excessive impulsivity. So it could be assumed that patients with a pre-operative lower FAB and Go-No Go test scores had a deficit of inhibitory control and thus a tendency to impulsivity, and that STN-DBS increased their impulsivity on both functional and dysfunctional dimensions. Indeed, low preoperative FAB score and low Go-No Go score were also associated with significant DI increase. This is in line with a result obtained in a study on genetic markers of striatal dopamine that showed a link between low stopping performance in a stop-signal task and a rise in DI [30]. A high preoperative UPDRS III score, reflecting the severity of the disease and the dopaminergic denervation, was associated with DI increase in univariate analysis. In our study, the multivariate analysis showed no relation between post-operative worsening of DI and the occurrence of preoperative ICD, suggesting that preoperative ICD do not predict the postoperative impulsivity outcome. On the reverse, highly impulsive patients preoperatively did not show postoperative ICD, which is in line with the argument of more complex reasons for occurrence of ICD. Indeed, impulse control disorders in the context of Parkinson's disease are considered as a mis-nomer contributing to a confusion with impulsivity. The hypo-hyperdopaminergic axis, the social context and the expectations of the entourage seem to be important factors to integrate while evaluating ICD, more than impulsivity itself (25). Further researches would be needed to investigate this absence of direct relation between ICD and impulsivity.

Concerning the clinical management of this post-operative ICD and DI variations, as well as for motor symptoms, changes in the stimulation parameters and in dopaminergic pharmacotherapy has been made by the neurologist in charge, with the help in some situations of the psychiatrists of our institution.

Finally we observed an association between DI increase and the location of the left stimulating lead contact in the ventral part of the STN. This observation is concordant with other observations studying the behavioural effects of STN-DBS according to the electrode location. Thus, Mallet et al reported in 2 PD patients that hypomania may be induced by stimulation of the ventral STN more likely than stimulation of dorsal STN which has been confirmed in larger studies [2, 31, 32]. Furthermore, neuropsychiatric outcomes after a STN-DBS within more ventromedial regions of this nucleus have been described [33]. A recent study about the impact of STN-DBS on ICD found no relation between the appearance and worsening of ICD and the active lead contact location according to the antero-posterior functional subdivisions of the STN based on the Yelnik & Bardinet atlas [34]. Similarly, we observed no relation between contact location according to this antero-posterior STN segmentation and ICD or impulsivity change. However this atlas has several limitations: it is based on a unique specimen, with its own specificities, which could present differences with our patients anatomy; also, functional subdivisions of the STN are expressed by homology with the monkey, as they don't appear with coloration in the human brain; last point, even if the resolution degree is high (1mm), a difference is still possible between the real localization of the stimulating contacts and the localization showed by the atlas. Nevertheless this atlas has been used in many studies and is considered as quite reliable. To overcome these limitations, we additionally decided to divide the STN into quadrants to analyse the contact location not only according to the atlas functional STN sub-divisions, but also relative to its position within the STN.

In our study, impulsivity changes were related to contact location according to ventro-dorsal STN segmentation, namely location of active contact in the ventral, presumed

limbic, part of the STN. The more anterior and ventral part of the STN are likely connected to limbic networks and DBS of this STN region has been shown to be efficient to treat obsessive-compulsive disorders which are characterized by a decreased impulsivity [23, 35]. Hershey et al reported that ventral STN-DBS altered Go-No Go responses suggesting that STN was involved in the balance between appropriate selection and inhibition of prepotent responses in cognitive paradigms [24]. However, the mechanisms underlying the onset of psycho-behavioral disorders, like ICD, after STN-DBS are complex and may depend on many factors (hypo-hyperdopaminergic axis, inter-individual mesolimbic denervation, location of stimulating contacts, ...)(25). Thus the stimulation of the ventral part of the STN does not seem to be the only factor explaining postoperative DI increase.

5. CONCLUSION

In this study, impulsivity changes after STN-DBS in PD patients were distinguished according to functional and dysfunctional dimensions of impulsivity, as defined by Dickman. Our study suggests that the STN-DBS would have different impacts on these two dimensions of impulsivity, worsening pathological impulsivity without altering physiological impulsivity. The increase in dysfunctional impulsivity could be promoted by the location of the electrode in the ventral part of the STN and preoperative alteration of the frontal functions. At-risk patients should be given greater attention by multidisciplinary teams after surgery, including a more systematic and timely postoperative psychiatric evaluation.

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TABLE AND FIGURE LEGENDS

Table I: Characteristics of 33 patients with Parkinson's disease before DBS-STN. UPDRS III: Unified Parkinson's Disease Rating Scale motor assessment. MADRS: Montgomery and Asberg Depression Rating Scale. FAB: Frontal Assessment Battery. DRS: Mattis dementia rating scale. LED: Levodopa-Equivalent Dose.

Table II: Changes in Dickman Impulsivity Inventory Functional Impulsivity (FI) and Dysfunctional Impulsivity (DI) sub-scores in 33 patients before and after STN-DBS.

Table III: Factors associated with significant increase of functional (FI) and dysfunctional (DI) impulsivities in patients treated by STN-DBS. FAB: Frontal Assessment Battery. UPDRS III: Unified Parkinson's Disease Rating Scale motor assessment. OR=Odd ratio. 95%CI=95% confidence interval. * : out of model $p > 0.15$

Figure 1: Location of stimulating active lead contacts according to changes in dysfunctional impulsivity (DI). A: Fusion of a postoperative MRI on the 3D atlas of the basal ganglia (lateral view) showing the lead contacts (blue) in the subthalamic nucleus (STN). Functional subdivisions according to the Yelnik & Bardinet atlas are displayed in colours, from posterior to anterior: sensory-motor (green), associative (purple), limbic (yellow). White lines indicated the 2 planes used additionally to segment the STN into quadrants: ventral and dorsal, lateral and medial, anterior and posterior. B-C: 3D postero-superior view of the STN showing locations of the contacts of patients without (B) and with (C) significant DI changes. DI increase was associated with location of the left contact in the ventral STN.

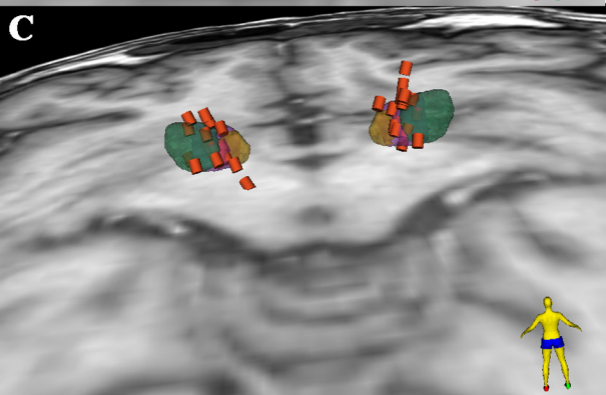
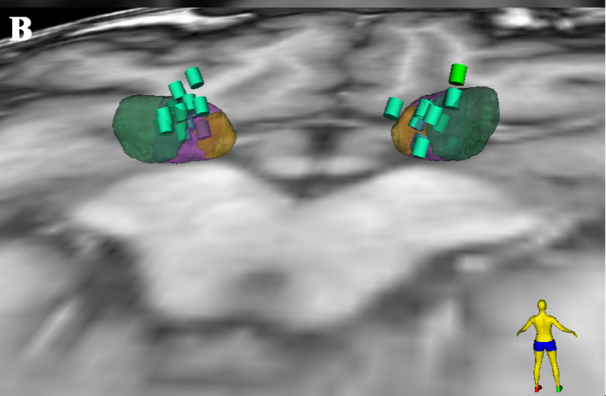
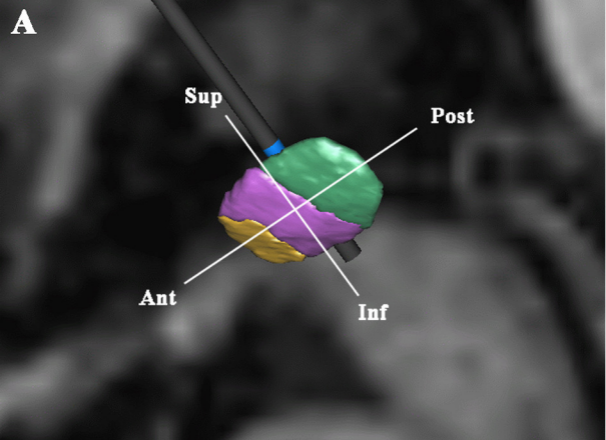


Table I: Characteristics of 33 patients with Parkinson's disease before DBS-STN. SD: Standard deviation. UPDRS III: Unified Parkinson's Disease Rating Scale motor assessment. MADRS: Montgomery and Asberg Depression Rating Scale. FAB: Frontal Assessment Battery. DRS: Mattis dementia rating scale. LED: Levodopa-Equivalent Dose.

	Mean	SD
Age	59	9,2
UPDRS III off-medication	38.2	10.0
UPDRS III on-medication	14.6	5.96
MADRS score	8.18	6.8
Apathy inventory score	2.75	5.3
FAB score	16.1	1.8
DRS score	136.7	6.4
Medication (LED)	1218	330.7
	Male	Female
Sex	20	13

Table II: Changes in Dickman Impulsivity Inventory Functional Impulsivity (FI) and Dysfunctional Impulsivity (DFI) sub-scores in 33 patients before and after STN-DBS.

	Before DBS		After DBS		Difference	p
	Mean	SD	Mean	SD		
FI	6.24	2.68	5.75	2.61	-0.05	0.33
DFI	1.93	1.64	3.48	2.40	1.54	<0.001

Table III: Factors associated with significant increase of functional (FI) and dysfunctional (DI) impulsivities in patients treated by STN-DBS. FAB: Frontal Assessment Battery. UPDRS III: Unified Parkinson’s Disease Rating Scale motor assessment. OR=Odd ratio. 95%CI=95% confidence interval. * : out of model p>0.15.

	Univariate			Multivariate		
	OR	95% CI	p-value	OR	95% CI	p-value
<u>Increased DI score ≥ 2</u>						
Left contact in ventral STN	0.159	0.0327 - 0.773	0.03	0.027	0.0015 - 0.458	0.012
Preoperative FAB score	1.514	0.904 - 2.535	0.1	2.539	1.094 - 5.891	0.03
Age	0.928	0.838 - 1.028	0.13	0.833	0.685 - 1.011	0.066
Preoperative UPDRS III <i>on med</i>	0.813	0.682 - 0.970	0.02	*	*	*
<u>Increased FI score ≥ 2</u>						
Preoperative apathy	1.165	0.985 – 1.378	0.07	1.146	0.983 – 1.336	0.08
Preoperative FAB score	0.587	0.328 – 1.050	0.07	0.602	0.331 – 1.10	0.10